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Neurogenic Obesity-Induced Insulin Resistance and Type 2 Diabetes Mellitus in Chronic Spinal Cord Injury

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The population with SCI is at a significant risk for both insulin resistance and type 2 diabetes mellitus (T2DM) secondary to neurogenic obesity. The prevalence of insulin resistance and T2DM in persons with SCI suggests that disorders of carbohydrate metabolism are at epidemic proportions within the population. However, the true frequency of such disorders may be underestimated because biomarkers of insulin resistance and T2DM used from the population without SCI remain nonspecific and may in fact fail to identify true cases that would benefit from intervention. Furthermore, diet and exercise have been used to help mitigate neurogenic obesity, but results on disorders of carbohydrate metabolism remain inconsistent, likely because of the various ways carbohydrate metabolism is assessed. The objective of this article is to review current literature on the prevalence and likely mechanisms driving insulin resistance and T2DM in persons with SCI. This article also explores the various assessments and diagnostic criteria used for insulin resistance and T2DM and briefly discusses the effects of exercise and/or diet to mitigate disorders of carbohydrate metabolism brought on by neurogenic obesity. **Key words:** *adipose tissue, diabetes mellitus, exercise, impaired glucose tolerance, insulin resistance, neurogenic obesity, spinal cord injury*

Introduction

Following a spinal cord injury (SCI), drastic alterations occur in body composition and cardiometabolic health.[1-6] Injury-induced changes result in a sedentary lifestyle, an obligatory sarcopenia, the accumulation of adipose tissue, skeletal muscle infiltration of intramuscular fat (IMF), and a decrease in energy expenditure marked by a reduction in fat free mass (FFM) and metabolic rate.[1,7-9] These changes consequently manifest as neurogenic obesity.[1]

Neurogenic obesity can lead to chronic, systemic inflammation that directly influences glucose homeostasis.[1,10,11] Adipose tissue-derived proinflammatory adipokines, tumor necrosis factor-α, and interleukin 6, lead to the upregulation of the transcription factors SOCS3 and STAT3, thereby inhibiting the phosphorylation of the insulin receptor substrate 1 and subsequently the phosphatidylinositol 3-kinase-protein kinase B signaling cascade in muscle and adipose tissue.[1,11] Other proinflammatory molecules also activate intracellular stress signaling pathways that lead to the secretion of non-esterified fatty acids (NEFAs) from visceral adipose tissue (VAT).[1,11] NEFAs interfere with cellular homeostasis by depositing in skeletal muscle and liver, preventing intracellular transport of plasma glucose[1,11] and promoting insulin resistance and type 2 diabetes mellitus (T2DM). Several studies have reported that greater quantities of adipose tissue in persons with SCI are linked with glucose intolerance and insulin resistance, both of which play a vital role in the development of T2DM.[6,12-14]

The objective of this monograph is to review the literature on the prevalence and mechanisms driving insulin resistance and T2DM in persons with SCI. This article also explores the various assessments and diagnostic criteria used for insulin resistance and T2DM and briefly discusses the effects of exercise and/or diet to mitigate these disorders of cardiometabolic dysfunction brought on by neurogenic obesity.

Insulin Resistance and Type 2 Diabetes Mellitus After Spinal Cord Injury

Insulin resistance is the state in which muscle, fat, and liver cells have a decreased response to

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endogenous and exogenous insulin, resulting in greater amounts of insulin secreted by the beta cells in the islets of Langerhans of the pancreas for adequate uptake of glucose into cells.[15-17] This retention of glucose in the blood leads to hyperglycemia and, over time, can lead to serious systemic damage including injury of the heart, kidneys, blood vessels, and eyes.[16-18] T2DM is defined by this chronic elevation in blood glucose levels secondary to insulin resistance. At earlier stages of insulin resistance, blood glucose levels are higher than the normal range **(Table 1)** but are not high enough to be diagnosed with T2DM. This intermediate state is referred to as prediabetes, also called impaired glucose tolerance.[15-18] In adults with SCI, screening for prediabetes and T2DM is conducted upon discharge from initial rehabilitation following injury and, if negative, repeated every 3 years thereafter.[19-22] The diagnosis of prediabetes and T2DM is made according to the criteria established by the American Diabetes Association **(Table 1)** for fasting plasma glucose (FPG), 2-hour plasma glucose during an oral glucose tolerance test (OGTT), or hemoglobin A1c (HbA1c).[19-22] These three tests have high sensitivity and specificity for the diagnosis of T2DM in the general population (HbA1c sensitivity 78%-81%, specificity 79%-84%; FPG, sensitivity 93.5%, specificity 99.7%; OGTT, sensitivity 97%, specificity 100%),[23,24] but they lack correlation in persons with SCI.[19-21,25,26] And so, selection of the most appropriate diagnostic evaluation, as well as changes in screening schedule, is based on clinician experience.[19-22,25,26] This lack of correlation is possibly due to the methods by which HbA1c, OGTT, and FPG establish the diagnosis T2DM. Whereas HbA1c is a measurement of chronic glycemic levels, OGTT and FPG view glucose levels at a single snapshot of time. Moreover, persons with SCI can experience postprandial hyperglycemia but remain euglycemic while fasting, leading to possible elevated glucose levels on an OGTT but normal results on HbA1c or FPG.[21,25] Additional research is needed to determine how best to reconcile this lack of correlation among the three tests.

The statistics on disorders of carbohydrate metabolism in persons with and without SCI are staggering. The recent 2020 National Diabetes Statistics Report from the Centers for Disease Control and Prevention estimates that 10.5% of the United States population has diagnosed or undiagnosed diabetes (with a total cost of $327 billion for diagnosed diabetes in 2017), and 34.5% of all adults in the United States had prediabetes based on fasting glucose or HbA1C levels.[27] However, according to Saeedi et al.,[28] the global prevalence of adult diabetes and prediabetes were estimated at 7.5% and 9.3%, respectively. The 2020 National Diabetes Statistics Report also published that the 2018 incidence of diabetes was 6.9 per 1000 persons (or, 1.5 million new cases of diabetes).[27] Similarly, prior studies have reported that persons with SCI are at an elevated risk for developing insulin resistance and T2DM.[14,29-31] A venerable study noted that 40% of individuals with SCI were glucose intolerant and had elevated insulin levels.[13] Bauman and Spungen[12] demonstrated that compared to 6% in a nondisabled veteran control group, 22% of veterans with SCI were diabetic after undergoing an OGTT. Lavela et al.[14] reported a stepwise increase with aging in the prevalence of T2DM in veterans with SCI compared to the able-bodied population. Further studies in that veteran population have also shown that this impaired glucose tolerance is linked to an increased insulin response when compared to able-bodied controls.[12] Recently, Gater et al.[32] reported that 77% of veterans with SCI were classified as obese when using the SCI-specific body mass index (BMI) cutoff of 22 kg/m^2, and approximately 50% currently had or were previously diagnosed with T2DM. Similar to able-bodied individuals, veterans with SCI have a higher prevalence of T2DM and insulin resistance with BMI greater than 25 kg/m^2.[33] however, this prevalence of insulin resistance is three-fold higher in people with SCI and more severe in those 45 to 59 years of age.[14] Additionally, Cragg et al.[29] reported an odds ratio of 1.66 for T2DM in persons with SCI compared to individuals without SCI, even after adjusting for smoking status, hypertension status, BMI, daily physical activity, alcohol intake, and daily consumption of fruits and vegetables. Lai et al.[30] reported an adjusted hazard ratio (AHR) for T2DM was 1.33 times higher in individuals with SCI compared to those without SCI and identified an incidence rate of 22.1 compared to 17.2 per 10,000 person-years in individuals with SCI compared to those without

Table 1. Screening and assessment criteria for disorders of glucose dysfunction

Method	Reference ranges	Equation/mathematical model
Clinical markers of glucose metabolism		
Fasting plasma glucose[20,56]	Normal: < 100 mg/dL	N/A
	Prediabetes: 100–125 mg/dL	
	T2DM: ≥ 126 mg/dL	
2-hour plasma glucose oral glucose tolerance test[20,56]	Normal: < 140 mg/dL	N/A
	Prediabetes: 140–199 mg/dL	
	T2DM: ≥ 200 mg/dL	
Hemoglobin A1c[20,56]	Normal: < 5.7%	N/A
	Prediabetes: 5.7–6.4%	
	T2DM: ≥ 6.5%	
Indices of glucose metabolism		
Homeostasis model assessment of IR[56,59,106,107]	Normal: < 1.6	HOMA-IR = [($Insulin_{fasting}$ (μU/mL)) x ($Glucose_{fasting}$ (mmol/L))]/22.5
	Early hepatic IR:1.7-2.4	
	Significant hepatic IR: > 2.5	
Homeostasis model assessment 2 of IR[56,72-76a]	Normal: < 1.4	Online calculator[b]
	IR: ≥1.4	
Quantitative insulin-sensitivity check index[56,82,108]	Normal: > 0.339	QUICKI = 1/[Log (Insulinfasting (μU/mL)) + Log (Glucosefasting (mg/dL))]
	IR: <0.339	
Matsuda index[56,86,107]	Normal: >2.5	ISI(Matsuda) = 10,000/√[(fasting glucose (mg/dL) x fasting insulin (μU/mL) x (mean glucose x mean insulin)][c]
	Peripheral IR: <2.5	
Gold standard assessments of glucose metabolism		
Euglycemic hyperinsulinemic clamp[56]	No reference ranges for M-value (glucose disposal rate) and insulin sensitivity (M-value/insulin)	SI_{clamp} = M/(G x ΔI); where GIR = M[d]
Intravenous glucose tolerance test[20,55]	No reference ranges for insulin sensitivity or glucose effectiveness	Minimal model proprietary software

Note: IR = insulin resistance; ISI = insulin sensitivity index; N/A = nonapplicable; T2DM = type 2 diabetes mellitus.

[a]There are currently no universal cutoff points to define normal versus abnormal HOMA2 values,[72] but several studies examining the general adult populations of Brazil,[73] Iran,[74] Turkey,[75] and Kuwait[76] have independently reported that a HOMA2 value of 1.4 is the optimal cutoff point to identify persons with insulin resistance.

[b]Online HOMA2 calculator downloaded from https://www.dtu.ox.ac.uk/homacalculator/

[c]Mean glucose and insulin values determined by plasma glucose and insulin values at 0, 30, 60, 90, 120 minutes of test.

[d]Average glucose infusion rate, where SI_{clamp} is insulin sensitivity from the clamp and M is normalized for glucose steady-state blood glucose concentration (G) and the difference between fasting and steady-state plasma insulin concentrations (ΔI).

SCI, respectively. The same authors further revealed that when examining men with SCI the AHR was 1.23, for adults ≥65 years old with SCI the AHR was 4.26, persons with complete paraplegia had an AHR of 2.13, and when having preexisting comorbidity the AHR was 1.36.[30] Moreover, studies in the United States demonstrate a prevalence of T2DM of 16% to 33% compared to an international prevalence of 6% to 14% in persons with SCI.[29,34-37] Several of the aforementioned studies[29,35-37] examined T2DM in specific countries (e.g., Canada, Taiwan, Japan, and the United States), but the reports did not indicate if the authors controlled for country-specific rates of T2DM. Consequently, the "true" prevalence of T2DM after SCI remains in question given that country-specific rates of T2DM vary, but generally speaking the value exceeds that of the population without SCI and warrants research to study what factors contribute most significantly to this difference.

Previous research[10,38,39] **(Table 2)** has documented the relationship between adipose tissue and measures of carbohydrate metabolism after SCI. Gorgey et al.[38] studied 13 persons with traumatic motor complete SCI to better understand the influence of VAT and subcutaneous adipose tissue (SAT) on cardiometabolic profiles after SCI. The authors demonstrated in the study cohort that increased VAT, SAT, and VAT/SAT were significantly more likely to have abnormal cardiometabolic profiles exhibiting impaired glucose tolerance, insulin resistance, and dyslipidemia.[38] Further analysis revealed a negative relationship between cross-sectional area (CSA) of VAT and fasting plasma insulin, suggesting increasing adiposity may be associated with a state of insulin resistance.[38] Jones and Legge[40] found that increased adiposity in persons with SCI compared to able-bodied controls was associated with disturbances in skeletal muscle-fatty acid metabolic processes that increase the risk of developing insulin resistance and ultimately metabolic syndrome. Furthermore, Rankin et al.[10] reported an association between liver adiposity, as measured by fat signal fraction, and fasting glucose HbA1c. Thus, higher levels of visceral, subcutaneous, and liver adipose tissue are associated with dysfunctional cardiometabolic profiles.

After an SCI, skeletal muscle undergoes profound atrophy below the level of injury, losing up to 45% of CSA in just 6 weeks after injury.[11,41-43] This change is associated with greater IMF accumulation when compared to individuals without SCI.[39,43,44] Using magnetic resonance imaging, Gorgey et al.[42] measured the CSA of thigh skeletal muscle in six persons with incomplete SCI. At 6 weeks post injury, persons with SCI were found to have a three-fold increase in IMF when compared to individuals without SCI matched for gender, age, height, and weight. This accretion of IMF was reported to increase further with additional time. Three months following the injury, the amount of IMF had risen another 26% since the 6-week measurement.[42] Furthermore, Elder et al.[39] reported that in individuals with complete SCI, the percentage of IMF is significantly correlated with plasma glucose and insulin levels as measured by OGTT, and Goodpasture et al.[44] demonstrated that IMF has a strong negative correlation with insulin sensitivity. Collectively, these data indicate IMF likely plays a critical role in carbohydrate metabolism after SCI.

Whereas higher levels of SCI have been associated with more favorable changes in lipid profiles through reduced total cholesterol low-density lipoprotein,[45,46] multiple studies have shown higher levels of injury to be related with negative effects in carbohydrate profiles.[4,47,48] Li et al.[47] reported that glucose, insulin, and C-peptide concentrations during an OGTT were higher in women with tetraplegia versus women with paraplegia and able-bodied women controls. In addition, women with tetraplegia had a significantly lower Matsuda insulin sensitivity index versus able-bodied women.[47] Farkas et al.[4] demonstrated a significantly elevated fasting glucose among individuals with tetraplegia compared to paraplegia. The same authors noted greater insulin sensitivity, as measured by intravenous glucose tolerance test (IVGTT), among individuals with paraplegia compared to tetraplegia. Similarly, Gorgey et al.[48] demonstrated that in persons with SCI in a response to a 2-hour OGTT, glucose area-under-curve was 24% higher in persons with tetraplegia compared to paraplegia. These findings are also supported by an early investigation by Bluvshtein et al.[49] Earlier research has suggested that the influence of level of injury on plasma glucose and insulin is a result of

Table 2. Summary of nonexercise literature examining carbohydrate metabolism after SCI

Author, year	Sample size (*n*) and demographics	Injury characteristics	Outcome measures	Main results
Bauman and Spungen, 1994[12]	• *n*=150 • SCI, *n*=100; AB, *n*=50 • 150 male, 0 female • Age: TSCI, 47±2 y; PSCI, 51±2 y; AB, 51±2 y	• Chronic motor complete SCI • TSCI, *n*=50; PSCI, *n*=50	• Prevalence of T2DM via OGTT • PI and PG via OGTT • Si via OGTT • VO2max • %FM and %FFM via DXA	• On OGTT, 22% of SCI had T2DM compared to 6% in AB • SCI had significantly ↑ mean PG and PI at several points during OGTT • Mean FG for SCI and AB were significantly ↑ in subjects with T2DM than with those with normal glucose tolerance • Si linearly correlated with VO2max but no correlation with %FM or %FFM
Bluvshtein et al., 2010[49]	• *n*=31 • SCI, *n*=18; AB, *n*=13 • TSCI, 11 male, 0 female; PSCI, 6 male, 1 female; AB, 9 male, 4 female • Age: TSCI, 42±8 y; PSCI, 33±10 y; AB, 34±13 y	• Chronic motor complete SCI • TSCI, *n*=11; PSCI, *n*=7 • AIS: A and B • LOI: TSCI, C4-C7; PSCI, T4–T6	• Plasma glucose and insulin levels following standardized meal • IR via postprandial glucose and insulin levels	• Postprandial IR found in TSCI but not PSCI, suggesting ↑ in postprandial insulin levels related to concomitant changes in sympathovagal balance
Castro et al., 1999[43]	• Data unavailable	• Data unavailable	• Skeletal muscle CSA of leg and thigh via MRI	• Average CSA of quadriceps femoris, the hamstring muscle group, and the adductor muscle group ↓ by 16%, 14%, and 16%, respectively • Average CSA of gastrocnemius and soleus ↓ by 24% and 12%, respectively; but no change in CSA of tibialis anterior
Chung et al., 2014[36]	• *n*=239,580 • SCI, *n*=47,916; AB, *n*=191,664 • SCI, 30,036 male, 17880 female; AB, 120,144 male, 71,520 female • Age: SCI, 50±19.9 y; AB, 49.5±19.9 y	• Data unavailable	• Prevalence of T2DM	• Prevalence of T2DM is 11% in SCI and 4.24% in general population of Thailand
Cragg et al., 2013[29]	• *n*=60,678 • SCI, *n*=297; AB, *n*=60,381 • 29,908 male, 30,770 female • Age: 40-44 y	• Data unavailable	• Prevalence of T2DM	• Prevalence of T2DM was 13.66% in SCI and 5.91% in AB • The odds of T2DM was 1.66 times ↑ in individuals with SCI versus AB after adjusting for sex and age

Author, year	Sample size (*n*) and demographics	Injury characteristics	Outcome measures	Main results
Duckworth et al., 1983[13]	• Data unavailable	• Data unavailable	• Prevalence of hyperglycemia • Glucose levels on OGTT	• 23% of consecutive discharges from a large SCI service had fasting hyperglycemia • 30% of stable SCI patients had glucose values greater than 200 mg/dL and additional 40% had values exceeding 140 mg/dL at 2-hour mark of OGTT • More than 40% of a group of glucose-intolerant SCI patients had ↑ insulin levels, suggesting tissue resistance to endogenous insulin
Duckworth et al., 1980[66]	• *n*=45	• AIS: A and B	• Plasma glucose and insulin levels on OGTT • Peripheral IR via OGTT	• Subjects with glucose intolerance had significantly ↑ insulin levels than glucosetolerant or healthy subjects • Subjects with glucose intolerance had significantly ↓ IR than other subjects
Elder et al., 2004[39]	• *n*=21 • SCI, 10 male, 2 female; AB, 3 male, 6 female • Age: SCI, 40±12 y; AB, 29±9 y	• Chronic motor complete SCI • TSI: 8±5 y	• OGTT • MRI of thighs	• Glucose and insulin levels on OGTT ↑ in SCI • IMF good predictor of glucose levels on OGTT • IMF percentage approximately 4-fold ↑ in thighs of SCI versus AB
Farkas et al., 2019[3]	• *n*=47 • 38 male, 9 female • Age: male, 44.9±10.9 y; female, 42.0 ± 13.5 y	• Chronic motor complete SCI • TSI: male, 15.2±11.0y; female, 10.9 ± 11.1y • LOI: male, C4–L1; female, C4–T11	• Sg and Si via IVGTT • VAT, SAT, and TTAT via MRI	• No difference in Sg or Si between males and females • VAT and VAT:SAT ratio were significantly ↑ in males • SAT volume significantly ↑ in females • No difference in TTAT between males and females
Farkas et al., 2018[4]	• *n*=47 • 38 male, 9 female • Age: 43.8±11 y	• Chronic motor complete SCI • TSCI, *n*=12; PSCI, *n*=35 • TSI: TSCI, 16.19±11.88 y; PSCI, 13.84±11.55 y • LOI: TSCI, C4-C8; PSCI, T2-L1	• Glucose and insulin levels via IVGTT • Si and Sg via IVGTT • Volume of VAT and SAT via MRI	• FG significantly ↓ in PSCI compared to TSCI • TSCI had ↓ Si and Sg and significantly ↑ FG • VAT volume was greater in TSCI versus PSCI; however, significance lost after adjusting for age
Gater et al., 2019[32]	• *n*=473 • 466 male, 7 female • Age: 56.0±13.1 y	• Chronic SCI • AIS: A, *n*=217; B, *n*=71; C, *n*=65; D-E, *n*=120 • TSCI, *n*=234; PSCI, *n*=233 • TSI: 19.2±9.4 y • LOI: TSCI, *n*=234; T1-T6, *n*=84; ≤T6, *n*=154	• Prevalence of T2DM • Prevalence of obesity, defined as BMI ≥30 kg/m^2 and the SCI-specific cutoff of BMI >22 kg/m^2	• Odds of T2DM were 1.93 and 2.09 times ↑ for obese patients than the odds of diabetes for nonobese patients using criteria of BMI ≥22 kg/m^2 and BMI ≥30 kg/m^2, respectfully • 77% of subjects classified as obese when using the SCI-specific BMI cutoff of 22 kg/m^2 and approximately 50% of subjects had or were previously diagnosed with T2DM
Gorgey et al., 2011[38]	• *n*=13 • 13 male, 0 female • Age: 35±8 y	• Chronic motor complete SCI • AIS: A and B • TSI: >1 y • LOI: C5-T11	• Volume, CSA, and percentages of VAT and SAT via MRI • Glucose tolerance and insulin resistance via OGTT • Plasma glucose and insulin levels on OGTT	• ↑ VAT, SAT, and VAT/SAT were significantly more likely to have impaired glucose tolerance and IR • VAT CSA negatively related to FI and positively related to FG • Trunk %SAT negatively associated with glucose AUC during OGTT

Author, year	Sample size (*n*) and demographics	Injury characteristics	Outcome measures	Main results
Gorgey and Dudley, 2006[42]	• *n*=12 • AB, 4 male, 2 female • Age: SCI, 28±4 y; AB, 29±4 y	• Chronic incomplete SCI • AIS: B and C • TSI: 6 weeks then 3 months	• Thigh skeletal muscle CSA via MRI • Thigh IMF CSA via MRI	• IMF was 3-fold ↑ in SCI group versus AB • After 3 months, IMF ↑ 26% in the SCI group compared to the measurement at time of injury
Gorgey et al., 2013[48]	• *n*=13 • 13 male, 0 female • Age: TSCI, 35.5±8 y; PSCI, 35±9 y	• Chronic motor complete SCI • TSCI, *n*=6; PSCI, *n*=7 • AIS: A and B • TSI: TSCI, 16±7 y; PSCI, 8.5±8 y • LOI: TSCI, C5-C7; PSCI, T4-T11	• Plasma glucose and insulin levels via OGTT • CSA of VAT and SAT via MRI	• No difference in CSA of VAT between TSCI and PSCI • VAT CSA associated with impaired FG and nonsignificantly with glucose AUC in TSCI and PSCI • LOI does not appear to influence distribution of VAT and SAT
Gorgey et al., 2017[65]	• *n*=16 • 8 male, 8 female • Age: male, 37.5±9 y; female, 39±13 y	• Chronic motor complete SCI • AIS: A and B • TSI: male, 11±10.75 y; female, 10±10.5 y • LOI: male, C7-T9; female, C6-T11	• Volume and CSA of VAT and SAT via MRI • FG and Sg via IVGTT	• SAT CSA was 1.6-1.75 times ↑ in the upper and lower trunks in females compared to males • VAT CSA was 1.8-2.6 times ↑ in the upper and lower trunks in male versus female • VAT ↑ in male versus female after adjusting for body weight • Sg negatively related to lower trunk SAT
Gorgey & Gater, 2011[68]	• *n*=32 • 32 male, 0 female • Age: 36 ± 9 y	• Chronic motor complete SCI • TSCI, *n*=7; PSCI, *n*=25 • AIS: A and B • TSI: 1 y • LOI: C5 to T11	• FM and FFM via DXA • Plasma glucose and insulin levels via OGTT	• ↑ leg FM/trunk FM, leg FM/body FM, and lower trunk FM/body FM ratios in TSCI than PSCI • Glucose AUC positively related to leg FM but not to trunk or body FM
Gorgey et al., 2009[69]	• *n*=15 • 13 male, 2 female • Age: 38±8 y	• Chronic motor complete SCI • AIS A and B • TSI: 10±8 y • LOI: C6-T11	• Lower limb muscle spasticity via Modified Ashworth Scale • Daily dose oral baclofen • Energy expenditure (via resting metabolic rate) • FM, FFM • HOMA	• ↑ muscle activity via spasticity was associated with ↑ EE, insulin sensitivity, lipid profile, and increased FFM • No relationship was found between BMI and flexor or extensor spasticity
Gorgey et al., 2010[104]	• *n*=10 • 8 male, 2 female • Age: 33 ± 7 y	• Chronic motor complete SCI • TSI: >1 y • LOI: C6-T11	• Muscle Spasticity (knee extensors) via Modified Ashworth Scale • FM, FFM • EE via resting metabolic rate • FI, FG • Si via HOMA and Matsuda index	• ↑ spasticity associated with ↑ total %FFM, and ↓ %FM • ↑ FFM associated with ↑ EE • Trend present between ↑ %FFM and PG • ↑ spasticity associated with significant ↓ in PI but ↔ in Si via HOMA or Matsuda index
Imai et al., 1996[37]	• *n*=244 • 244 male, 0 female • Age: 49 y	• Chronic SCI • TSI: 17.3 y • LOI: C1-T5, *n*=23; T6-T10, *n*=30; T11-L1, *n*=173; L2-S5, *n*=18	• Prevalence of T2DM	• Prevalence of T2DM is 2.5-3.2 times ↑ than the general population of Japan

Author, year	Sample size (*n*) and demographics	Injury characteristics	Outcome measures	Main results
Jones et al., 2019[40]	• *n*=40 • SCI, *n*=20; AB, *n*=20 • 40 male, 0 female • Age: SCI, 33±2 y; AB, 33±2 y	• Chronic SCI • AIS: A, *n*=5; B, *n*=6; C, *n*=2 • TSI: 10.3±1.8 y • LOI: C4-L3	• Si via Matsuda index • IR via HOMA • FI, FG • FFM and FM of legs and trunk via DXA	• Significantly ↓ Si in SCI • No difference in HOMA-IR, FI, or FG between SCI and AB • ↑ FM and ↓ FFM in SCI
Karlsson, 1999[55]	• *n*=20 • Age: SCI, 39 y; AB, 33 y	• Chronic motor complete SCI • LOI: C6-T4	• Level of sympathetic disruption via plasma noradrenaline • FM via DXA scan • Glucose and insulin levels via OGTT • Insulin sensitivity via EHIC	• SCI displaying sympathetic nervous system dysfunction via ↑ noradrenaline spillover • SCI with ↑ insulin resistance and ↑ FM than AB
Lai et al., 2013[30]	• *n*=262,100 • SCI, *n*=28,696; AB, *n*=209,680 • 166,560 male, 95,540 female • Age: SCI, 51.7±18.3 y; AB, 51.6±18.3 y	• Chronic SCI • LOI: cervical SCI, *n*=28,696; complete thoracic SCI, *n*=274; incomplete thoracic SCI, *n*=6,073; lumbar-sacralcoccygeal SCI, *n*=17,279	• Incidence rate of T2DM • AHR of T2DM in SCI versus AB	• Per 10,000 person-y, T2DM incidence rate of 22.1 in SCI compared to 17.2 in AB • Cervical SCI, complete thoracic SCI, and incomplete thoracic SCI had a 20%, 135%, 60% ↑ risk of T2DM compared with AB • AHR for T2DM was 1.33 for SCI vs AB • AHR of T2DM was 1.23 for males with SCI vs women with SCI • For adults ≥ 65 y old with SCI the AHR of T2DM was 4.26 • AHR of T2DM was 2.13 in PSCI and 1.36 in subjects with preexisting comorbidity (hypertension, hyperlipidemia, stroke, coronary heart disease, congestive heart failure)
Li et al., 2019[47]	• *n*=42 • SCI, 0 male, 22, female; AB, 0 male, 20 female • Age: TSCI, 40.6±12.3 y; PSCI, 43.4±10.1 y; AB, 43.6±11.9 y	• Chronic motor complete SCI • TSCI, *n*=8; PSCI, *n*=14 • TSI: TSCI, 12.6±8.5 y; PSCI, 14.7±15.1 y	• Plasma glucose and insulin levels via OGTT • CRP • Si via Matsuda index • %FM, TBLM via DXA	• No difference in FG, FI, or CRP during OGTT among all three groups • After adjusting for TBLM and %FM, glucose and insulin at 2-hour mark of OGTT ↑ in TSCI vs PSCI and AB • Si ↑ in TSCI than in AB even after adjusting for TBLM
LaVela et al., 2006[14]	• *n*=18,759 • SCI, *n*=741; general veteran population, *n*=1,342; general population, *n*=16,676 • 18,384 male, 375 female • Age: 58 y	• Chronic SCI • TSCI, *n*=326; PSCI, *n*=415; • TSI: 21 y	• Prevalence of T2DM via OGTT	• Self-reported T2DM in veterans with SCI nearly 3-fold ↑ than general population but similar to that of general veteran population
Nash et al., 2016[85]	• *n*=389 • 329 male, 70 female • Age: 37.80±11.33 y	• Chronic SCI • TSCI, *n*=209; PSCI, *n*=180 • AIS: A, B, C, and D • TSI: 10.89±8.69 y • LOI: C1-L3	• Prevalence of cardiometabolic syndrome • IR via HOMA2 and QUICKI	• After adjustment for multiple comparisons, LOI and AIS grade unrelated to IR • IR significantly associated with cardiometabolic syndrome in HOMA2 and QUICKI models

Author, year	Sample size (*n*) and demographics	Injury characteristics	Outcome measures	Main results
Rajand et al., 2010[33]	• *n*=1938 • 1938 male, 0 female • Age: 55.5±12.58 y	• PSCI, *n*=1109	• BMI • Prevalence of T2DM after adjusting for age, race, tobacco use, and paraplegia/tetraplegia status	• Compared to normal weight subjects (BMI 18.50-24.99 kg/m^2), prevalence of T2DM is 50% ↑ in overweight subjects (BMI 25.00-29.99 kg/m^2) and about 3-fold higher in obese subjects (BMI ≥ 30.00 kg/m^2) • ↔ in the prevalence of T2DM for high normal weight (BMI, 23–24.99 kg/m^2) or low overweight (BMI, 25–27.49 kg/m^2) • Prevalence of T2DM was 2-fold ↑ among in subjects with BMI, 27.5–29.99 kg/m^2
Rankin et al., 2017[10]	• *n*=22 • 22 male, 0 female • Age: 36.1±10.0 y	• Chronic motor complete TSCI, *n*=8; PSCI, *n*=14 • TSI: 8.2±7.9 y • LOI: C5-T11	• Fat signaling fraction of liver adipose on MRI • Si and Sg via IVGTT • FG • VAT, SAT via DXA	• Fat signaling fraction positively related to FG, negatively related to Si, and no relationship to Sg • ↔ in inflammatory cytokines, trunk CSA, SAT, or VAT
Raymond et al., 2010[41]	• *n*=25 • 20 male, 5 female	• Chronic SCI • TSCI, *n*=11; PSCI, *n*=14 • High PSCI (T1-T5), *n*=8; Low PSCI (≤T6), *n*=6 • TSI: 11.0±7.6 y • LOI: C3/4 to T12	• Plasma glucose and insulin levels via 2-hour OGTT • Physical activity level via Physical Activity Scale for Individuals with Physical Disabilities (PASIPD)	• 36% of subjects had either impaired glucose tolerance or T2DM based on their 2-hour OGTT • All participants had normal FG • Physical activity level is a determinant of glucose tolerance, independent of the extent of neurological impairment
Raymond et al., 2010[99]	• *n*=25 • 20 male, 5 female • Ages: 37±9 y	• Chronic SCI • TSCI, *n*=11; PSCI, *n*=14 • TSI: >6 months • LOI: C3-T12	• FG • 2-hour PG on OGTT • Physical activity scale for individuals with physical disabilities	• Physical activity and age, but not lesion level were independent determinants of 2-hour OGTT results
Washman et al., 2010[35]	• *n*=1623 • SCI, *n*=135, general population, *n*=1488 • SCI, 104 male, 31 female • Age: SCI, 48±13.7 y	• Chronic SCI • AIS: A, *n*=109; B, *n*=13; C, *n*=10 • LOI: T1–T6, *n*=45; T7–T12, *n*=66; L1–L4, *n*=24 • TSI: 18.4±12.3 y	• Prevalence of T2DM	• Prevalence of T2DM is 6% in SCI vs 2.6% in general population of Sweden

Note: ↑ = increase; ↓ = decrease; ↔ = no change; AB = able-bodied controls; AIS = American Spinal Injury Association Impairment Scale (A: complete; B: sensory incomplete, C: motor complete, D: motor incomplete, E: normal); AHR = adjusted hazard ratio; AUC = area under the curve; BMI = body mass index; CRP = C-reactive protein; CSA = cross-sectional area; DXA = dual-energy x-ray absorption scan; EE = energy expenditure; FFM = fat-free mass; FG = fasting glucose; FI = fasting insulin; FM = fat mass; HOMA = homeostasis model assessment; HOMA2 = homeostasis model assessment-2; IMF = intramuscular fat; IR = insulin resistance; IVGTT = intravenous glucose tolerance test; LOI = level of injury; MRI = magnetic resonance imaging; OGTT = oral glucose tolerance test; PI = plasma insulin; PG = plasma glucose; PSCI = paraplegic spinal cord injury; QUICKI = quantitative insulin sensitivity check index; SAT = subcutaneous adipose tissue; SCI = spinal cord injury; Si = insulin sensitivity; Sg = glucose effectiveness; TTAT = total trunk adipose tissue; T2DM = type 2 diabetes mellitus; TBLM = total body lean mass; TSCI = tetraplegic spinal cord injury; TSI = time since injury; VAT = visceral adipose tissue; y = years.

sympathetic nervous system dysfunction following SCI.[49-51] Increased, not decreased, sympathetic nervous system activity is thought to contribute to insulin resistance by impairing glucose delivery via vasoconstriction[52,53] and by activating α1-adrenergic receptors in adipose tissue.[54] This was supported by Karlsson[55] who reported decreased insulin sensitivity on OGTT associated with increased sympathetic nervous system activity and vasoconstriction below the level of injury in seven people with SCI. Although more research is needed to determine the precise contribution of autonomic nervous system dysfunction, there is a strong association between higher LOI and greater levels of both glucose intolerance and insulin resistance.

Assessment of Insulin Resistance and Type 2 Diabetes Mellitus

To date, there are several methods of assessment for insulin resistance and T2DM that are used in both the able-bodied population and population with SCI **(Table 1).** These methods are detailed below along with the literature from both populations.

In order to estimate levels of insulin resistance and β-pancreatic function, methods such as the Matsuda index, the quantitative insulin sensitivity check index (QUICKI), and the homeostasis model assessment (HOMA) have been proposed. These models account for both baseline insulin and glucose levels, with HOMA and QUICKI assessing primarily hepatic insulin resistance, and the Matsuda index and OGTT evaluating peripheral tissue insulin resistance; nonetheless, they only reflect the association between insulin and glucose, but not the response to an insulin challenge.[56-60]

The gold standard for the assessment of glucose homeostasis is the euglycemic hyperinsulinemic clamp (EHIC).[56] First developed in 1979, the EHIC uses a constant insulin infusion to create a hyperinsulinemic steady state while a bedside analyzer monitors plasma glucose levels and 20% dextrose is given intravenously to maintain euglycemia.[56] The primary advantage of this method is that it measures whole body glucose tolerance, and it directly measures the effect of insulin to induce glucose utilization under steady-state conditions. However, the EHIC is rarely used in clinical settings because it is a time and labor-intensive test that requires a skilled technician and is also very costly.[56,57,61] The EHIC was utilized by Karlsson[55] to show the association between insulin resistance and autonomic nervous system dysfunction in people with SCI and by Mohr et al.[62] to demonstrate the improved insulin sensitivity in subjects with SCI who completed 1 year of functional electrical stimulation (FES) cycling three times per week. Because of this additional labor, time, and need for trained operators, the EHIC method is infrequently used in persons with SCI and is primarily reserved for research settings with relatively small populations where assessing insulin sensitivity is of primary interest.[56]

An alternative test is the 3-hour IVGTT, which is also known as the frequently sampled IVGTT. The IVGTT is less time- and labor-intensive compared to EHIC.[56,63] After an overnight fast, the test begins with a weight-based bolus of glucose given intravenously over 2 minutes, followed by an infusion of weight-based exogenous insulin 20 minutes later. Glucose and insulin levels are closely monitored over 3 hours via multiple blood samples. These data are subjected to the minimal model to calculate glucose effectiveness (Sg), the ability of glucose to stimulate its own uptake, and insulin sensitivity (Si), the ability of insulin to increase glucose uptake.[64] Studies using IVGTT by Farkas et al.[3,4] have shown lower fasting glucose levels in subjects with paraplegia compared to those with tetraplegia, but no significant differences in Sg or Si between men and women with SCI. In Gorgey et al.,[65] Sg on IVGTT was found to be negatively related to SAT, which was found to be significantly greater in women. These reports show that higher levels of injury tend to have higher levels of plasma glucose during an IVGTT and that, contrary to previous work by Gorgey et al.,[38] SAT may have some protective effect on cardiometabolic profile after SCI.

The OGTT is comparable to the IVGTT. The OGTT provides a standardized, non–weight-based glucose bolus that is administered orally rather than intravenously, and the blood levels are monitored over a 2-hour window rather than 3. Several studies have utilized OGTT in the population with SCI.[12,48,66-69] For the population with chronic SCI, the initial fasting glucose level may be within

normal limits,[66] and younger individuals with SCI have significantly higher sum plasma glucose levels over an OGTT when compared to nondisabled controls.[12,67] Studies utilizing OGTT have also shown that glucose levels are increased in subjects with higher levels of SCI,[48,68] and lower in subjects with elevated muscle activity, via spasticity.[69] Like the IVGTT, the OGTT is more appropriate for larger population studies when compared to the EHIC, and Nadon et al.[70] has shown that the OGTT is consistent with IVGTT in the diagnosis of T2DM in the nondisabled population. The OGTT does not, however, demonstrate true insulin sensitivity or resistance. Further studies are required to determine whether the OGTT or IVGTT is more accurate in the diagnosis of prediabetes and whether the two tests are consistent in the diagnosis of T2DM in the population with SCI.

The HOMA model of insulin resistance is a surrogate to the EHIC, IVGTT, and OGTT.[56,58-60] This index only requires fasting plasma glucose and insulin levels, making it more easily applicable for large epidemiological studies and clinical research studies.[56] This equation operates under the assumption of a feedback loop between glucose production in the liver and insulin levels dependent on pancreatic beta cell function.[56] Thus, the HOMA model functions as an estimate of hepatic insulin resistance but does not directly reflect response to an insulin challenge.[56,58-60] An updated version of the homeostasis model, called HOMA2, was later derived via computer simulations to better account for variations in hepatic and peripheral insulin resistance. HOMA2 also provides baseline estimates of insulin sensitivity and beta cell function from the fasting glucose and insulin values but does not reflect a response to an insulin challenge.[56,71] Unfortunately, when compared to EHIC and IVGTT, the HOMA2 model systematically underestimates insulin sensitivity while overestimating percentage of beta cell function.[71]

Although HOMA has an established reference range for adults **(Table 1)**, there is currently no universal cutoff point to define normal versus abnormal HOMA2 values.[72] However, several studies examining the general adult populations of Kuwait, Iran, Turkey, and Brazil have independently reported that a HOMA2 value of 1.4 is the optimal cutoff point to identify persons with insulin resistance.[73-76] These results differ from Bermudez et al.,[77] who identified a cutoff value of 2.0 in the Venezuelan general adult population. Interestingly, in a sample of 99 men with chronic SCI and 51 healthy male controls, Hobson et al.[78] reported an SCI-specific HOMA2 ≥1.65 to identify the risk of metabolic syndrome. Using this cutoff, the authors reported that 36% of the study participants with SCI were classified as insulin resistant. In a three-subject case series by Bigford et al.,[79] subjects with SCI who underwent a 6-month program of circuit resistance exercise and Mediterranean diet showed significant improvements in lipoprotein cholesterol profiles and insulin resistance measured by HOMA2. D'Oliveira et al.[80] examined the relationship between body composition and glucose tolerance in physically active and nonactive individuals with cervical SCI. The investigators found that HOMA2 indices and fasting plasma insulin levels improved as relative FFM increased and decreased as trunk fat mass rose. Moreover, in Maher et al.,[81] physically active individuals with chronic SCI were shown to have no benefit in glycemic control from using bionic exoskeletons. These reports[79-81] demonstrate that, based on the homeostasis models, improvements in diet and relative fat levels in the population with SCI are associated with enhancement of cardiometabolic profiles.

QUICKI also provides a reliable estimate for hepatic insulin sensitivity.[56,58,82] The method requires serial glucose and insulin samples before and after a standard sample of glucose. Insulin sensitivity and resistance calculated by QUICKI (r = 0.48, p < .01) and HOMA (r = -0.53, p < .001), respectively, have a comparable correlation with the EHIC.[83,84] However, the variability of QUICKI is significantly less (coefficient of variance [CV] = 3.9%) than the homeostasis model (CV = 26.7%).[83,84] This difference in variability is possibly due to the normalization by logarithmic transformation of the values in HOMA.[84] Like the homeostasis model, QUICKI is best suited for large epidemiologic and clinical research studies.[56,82] In a study by Nash et al.,[85] 32% of subjects in a pooled sample (n = 389) of individuals (males, n = 329 and females, n = 70; age 37.8 ±11.3) with SCI (paraplegia, n =180 and tetraplegia, n = 209) from seven clinical studies

were found to have significant insulin resistance by either HOMA2 or QUICKI. Although it has much less variability than HOMA, the QUICKI model is not commonly used because it is less well known and requires log transformation.[57]

Similar to the IVGTT and OGTT, the Matsuda index requires serial glucose and insulin samples before and after a standard dose of glucose. The Matsuda index requires glucose and insulin measurements to be taken every 30 minutes over 2 hours. Although, there is some evidence to suggest that as few as two time points (taken at the beginning and end of the test) can be sufficient for accurate results.[86,87] This method incorporates both hepatic and peripheral insulin sensitivity to create a whole body insulin sensitivity index, but it does not include response to an insulin challenge.[60] The Matsuda method is simpler to perform than the EHIC method but also retains good correlation with the clamp method.[56,86] In the chronic SCI population, Gorgey et al.[38] used HOMA and the Matsuda models to show elevated insulin resistance as VAT and SAT increased. Nightingale et al.[88] reported that a 6-week moderate-intensity exercise therapy improved participants' HOMA2 but not Matsuda indices, suggesting an enhancement in hepatic but not peripheral insulin resistance. Compared to the able-bodied controls, subjects with chronic SCI were found to have a reduction in whole body insulin sensitivity index values by up to 50%, as reported in Yarar-Fisher et al.[67] The Matsuda model is a strong model that allows investigators the opportunity to distinguish changes in baseline insulin resistance on a systemic level from alteration in solely hepatic insulin resistance.

The IVGTT, OGTT, and Matsuda index incorporate both peripheral and hepatic insulin sensitivity and generally correlate well with EHIC model estimates, but only the IVGTT reflects responses to an insulin challenge. These tests generally require more time and effort than models that rely on fasting blood samples.[56] Henriquez et al.[57] compared the variability among HOMA, HOMA2, QUICKI, and Matsuda in 80 healthy, non-SCI participants. The investigators reported that coefficient of variation was highest for HOMA and HOMA2 (>10%) and lowest for QUICKI (<3%), which also had a strong correlation with the results of the Matsuda index. However, the study's results were limited to the study population of healthy individuals.[57] These data[56,57] are important for clinicians and researchers to bear in mind as they interpret the results of these models.

For individuals with or without SCI, a diagnosis of T2DM or prediabetes in the clinical setting is usually determined through fasting glucose, 2-hour plasma glucose during OGTT, or HbA1c.[22,34,89,90] These results are based on glucose levels and, except for the OGTT, these tests do not provide information on insulin sensitivity. To date, more evidence is required to establish screening guidelines specific to people with SCI. The present recommendations by the Paralyzed Veterans of America suggest screening for T2DM in persons with SCI using the same criteria as established by the American Diabetes Association for the able-bodied population.[22,34,89] This screening includes FPG, HbA1c, or 2-hour OGTT every 1 to 3 years with test preference and frequency based on clinician experience.[19,20,22,34,89] Assessments should begin upon discharge from initial rehabilitation following SCI. For community-dwelling individuals, the current reference ranges and recommended frequency for diagnostic testing are similar to those for the population without SCI.[19,20,22,35,89] Additional studies are needed to see if these guidelines can be further tailored to level and completeness of injury for people with SCI.

Effect of Exercise on Insulin Resistance and Type 2 Diabetes Mellitus

Many studies have demonstrated the benefits of exercise in persons with SCI **(Table 3)**.[9,69,80,91-105] Both D'Oliveira et al.[80] and Koury et al.[91] examined the effects of physical activity in people with chronic SCI. Both studies demonstrated significant improvements in serum insulin levels and HOMA in subjects who were physically active for at least 150 minutes per week over the span of at least 3 months. This improvement in HOMA was also noted by Bakkum et al.[92] after persons with SCI completed two to three hand cycle or hybrid cycle sessions per week over 16 weeks and by Kim et al.[93] following a 6-week indoor hand-bike exercise program. Jeon et al.[96] reported that following 8 weeks of FES, glucose levels were reduced by 15.3%. Likewise, in subjects with chronic SCI who completed 8 to 10 weeks of

Table 3. Summary of exercise literature examining carbohydtrate metabolism after SCI

Author, year	Sample size (*n*) & demographics	Injury characteristics	Exercise modality	Carbohydrate metabolism	
				Outcome measures	Main results
Bakkum et al., 2015[92]	• *n*=19 • 18 male, 1 female • Age: 48±9 y	• Chronic SCI • AIS: A, B, C, and D • LOI: C3-T11	• Hybrid cycle, *n*=9; Hand cycle, *n*=10 • 18-32 min/session • 2 sessions/week • 16 week duration	• Pre and post-therapy IR via HOMA	• Both groups with significant ↓ in IR post-therapy
Bigford et al., 2014[79]	• *n*=3 • 3 male, 0 female • Age: 48±7 y	• Chronic motor complete SCI • AIS: A • PSCI, *n*=3 • TSI: 12.8±14.4 y • LOI: T3-T7	• Upper body circuit RT with Mediterranean diet • 6 month duration; then 6 month maintenance phase	• IR via HOMA	• IR ↓ in all 3 subjects after 6 months of therapy • ↓ IR maintained in 2 of 3 subjects during maintenance phase
Bresnahan et al., 2018[102]	• *n*=10 • 8 male, 2 female • Age: 36.7±12.5 y	• Chronic motor complete SCI • TSI: 0.6-34.0 y • LOI: C7-T5	• ACE • 30 min/session • 3 sessions/week • 10 week duration	• EE via resting metabolic rate • FG, FI, PG, and PI via OGTT • IR and pancreatic ß-cell activity via HOMA and • Si via HOMA and Matsuda Index	• Significant ↑ in FI, FI:FG ratio, and Si following therapy • ↔ in glucose AUC on OGTT, ß-cell activity, or EE from pre to post therapy • Significant ↑ in IR and Si via HOMA but not via Matsuda index
de Groot et al., 2003[98]	• *n*=6 • 4 male, 2 female • Age: 36±13 y	• Chronic SCI • AIS: A, B, C, D • TSI: 116±77 days • LOI: C5-L1	• ACE • 1 hour interval training • 8 week duration	• VO2Peak • Maximal power output • Insulin sensitivity via HOMA	• Positive correlation between VO2Peak and Si • ↑ in VO2Peak and maximal power output
D'Oliveira et al., 2014[80]	• *n*= 22 • n-PA, *n*=8; PA, *n*=14 • 22 male, 0 female • Age: n-PA, 35±12 y; PA, 29±8 y	• Chronic SCI • TSI: n-PA,14 ±10 y; PA, 8±7 y • LOI: C5-C7	• Self-reported physical activity duration and frequency via survey • 13.0±7.0 hours/week • 14.0±10.0 month duration	• Reported physical activity duration and frequency via survey • FM, FFM via DXA • FI and FG	• ↓ total FM, FM%, regional FM, FI levels and HOMA and ↑ total FFM, FFM%, and regional FFM in PA compared to n-PA • For n-PA, FPI and HOMA index negatively correlated with FFM% and positively correlated to trunk-FM
Gorgey et al., 2012[94]	• *n*=9 • Diet, *n*=4; RT+diet therapy, *n*=5 • Age: 35±9 y	• Chronic motor complete SCI • AIS: A and B • TSI: 13±9 y • LOI: C5–T11	• RT of the knee extensor muscle groups using neuromuscular electrical stimulation and ankle weights • 2 sessions/week • 12 week duration	• FG, FI • PG and PI during OGTT • Skeletal muscle mass of whole thigh, knee extensors/ flexors via MRI • IR via HOMA	• ↔ in FI and FG between groups pre therapy • No significant changes PI or Glucose AUC in diet and RT+diet • Glucose AUC adjusted to muscle mass higher pre therapy and had significant ↓ in the RT+diet , but ↔ in diet • ↔ in IR from pre to post therapy
Gorgey et al., 2017[103]	• *n*=9 • 9 males, 0 female • Age: 38±9 y	• Chronic motor complete SCI • TSI: 7±5 y • LOI: C5–T10	• FES-LEC, *n*=4; ACE, *n*=5 • 5 sessions/week • 16 weeks duration	• Vastus lateralis and triceps brachii muscle biopsies • GLUT4, AMPK, and PGC-1a • Fasting plasma glucose and insulin levels	• 2- to 4-fold ↑ in GLUT4, AMPK, and PGC-1a in muscles • ↔ in PG or PI following ACE or FES-LEC

Author, year	Sample size (*n*) & demographics	Injury characteristics	Exercise modality	Carbohydrate metabolism	
				Outcome measures	Main results
Griffin et al., 2009[97]	• *n*=18 • 13 male, 5 female • Age: 40±2.4 y	• Chronic SCI • TSI: 11±3.1 y • LOI: C4-T7	• FES-LEC • 2-3 sessions/week • 10 week duration	• PG, PI, and Si via OGTT • FM, FFM	• Significantly ↑ Si post therapy • ↑ in FFM associated with significantly ↓ PG and ↑ PI on OGTT following therapy
Jeon et al., 2002[96]	• *n*=7 • 5 male, 2 female • Age: 44.9±8.1 y	• Chronic motor complete SCI • TSI: 20.4±14.3 y • LOI: C5-T10	• FES-LEC • 30 min/session • 3 sessions/week • 8 week duration	• Plasma glucose levels on 2-hour OGTT • Insulin sensitivity via EHIC	• PG during OGTT ↓ by 15.3% • ↔ in Si
Kim et al., 2015[93]	• *n*=15 • n-PA, *n*=7; PA, *n*=8 • 9 male, 6 female • Age: n-PA, 35.0±5.1 y; PA, 31.5±5.5y	• Chronic motor complete SCI • AIS: A, *n*=7; B, *n*=8 • TSI: n-PA, 8.2±4.4 y; PA, 5.0±3.2 y • LOI: C5-T11	• Hand-bike exercise program • 1 hour/session • 3 sessions/week • 6 week duration	• FI • IR via HOMA • Percent body fat and lean mass via DXA	• FI, IR, and percent body fat reduced by 37%, 40%, and 9%, respectively in PA following therapy • Lean mass increased by 7.4% in PA following therapy
Koury et al., 2015[91]	• *n*=22 • n-PA, *n*=9; PA, *n*=13 • 22 male, 0 female • Age: 33.7±9.9 y	• Chronic motor complete SCI • TSI: 11.6±8.7 y • LOI: C5-C7	• Self-reported physical activity duration and frequency via survey • ≥150 total min/week • ≥3 exercise sessions/week • ≥3 consecutive month duration	• Reported physical activity duration and frequency via survey • PI • IR via HOMA	• PI and HOMA inversely proportional to the time of physical activity • PA had ↓ levels of PI and HOMA compared to n-PA
Maher et al., 2020[81]	• *n*=20 • SCI, *n*=10; AB, *n*=10 • Age: SCI, 32.9±11.4 y; AB, 29.5±7.7 y	• Chronic SCI • AIS: A, B, and C • TSI: 23.8±7.5 y • LOI: C7-T1	• 45 min of outdoor bionic ambulation • 2-4 week duration	• EE* at seated, standing, and during therapy • Posttherapy PG and PI via OGTT • HOMA2 via OGTT	• EE was ↑ in controls than the SCI group when standing and walking, but ↔ when sitting • Postbionic ambulation, glucose AUC with nonsignificant ↓ and requiring 20% ↓ insulin than at rest • ↔ in HOMA2 from baseline to post therapy
Mohr et al., 2000[62]	• *n*=10 • 8 male, 2 female • Age: 35±2 y	• Chronic SCI • TSI: 12±2 y • LOI: C6–T4	• FES-LEC • 30 min/session • 3 sessions/week • 1 y duration with 7 subjects receiving additional 6 months of reduced therapy (1 day/week)	• Si via OGTT • PG and PI via EHIC and OGTT • GLUT4 levels via muscle biopsies of vastus lateralis	• Insulin-stimulated glucose uptake rates ↑ at 1 y mark • Si returned to baseline during reduced therapy period • GLUT4 ↑ by 105% at 1 y mark and returned to baseline during reduced therapy period • ↔ in glucose tolerance or insulin responses to OGTT post therapy

Author, year	Sample size (*n*) & demographics	Injury characteristics	Exercise modality	Carbohydrate metabolism: Outcome measures	Carbohydrate metabolism: Main results
Nightingale et al., 2017[88,101]	• *n*=21 • 15 male, 6 female • Age: control, 48±10 y; ACE, 46±6 y	• Chronic SCI • AIS A-B, *n*=18; C-D, *n*=3 • TSI: control, 20±10 y; ACE, 14±11 y • LOI: control, T4-L3; ACE, T4-L1	• ACE • 45 min/session • 4 sessions/week • 6 week duration	• Pancreatic ß-cell function by HOMA2 • Plasma insulin and glucose levels during OGTT • Composite insulin sensitivity index via Matsuda inde	• FI ↓ by 14% and ß-cell function ↑ by 24% in ACE • ↔ in FG
Ryan et al., 2013[105]	• *n*=14 • 11 male, 3 female • Age: 26.7±4.7 y	• Chronic motor complete SCI • TSI: 7.7±6.5 y • LOI: C4-T7	• Electrically induced resistance exercise training of knee extensors • 2 sessions/week • 16 week duration	• FG • IR via HOMA • OGTT • Muscle mass volume in quadriceps and hamstring muscles via MRI • IMF volume in quadriceps and hamstring muscles via DXA	• ↔ in FG or IR • ↔ in 2-hour PG or 2-hour PI after therapy on OGTT • Significant ↑ in muscle mass of quadriceps but nonsignificant ↑ in hamstring muscle mass • ↔ IMF in either quadriceps or hamstring muscles
Yarar-Fisher et al., 2013[67]	• *n*=24 • SCI, n = 12; AB, n =12 • 24 male, 0 female • Age: SCI, 49.6±10 y; AB, 42.1±11.3 y	• Chronic motor complete SCI • AIS: A and B • TSI: 22±10 y • LOI: C5-T8	• Isometric lower extremity NMES-RE • 90 isometric contractions of quadriceps muscle • 1 session duration	• OGTT • Levels of glucose transport proteins (GLUT4, CaMKII PKB/Akt, and AMPK) via biopsy of vastus lateralis muscles	• Impaired glucose tolerance via ↑ PG in SCI via compared to AB at all time points during OGTT • GLUT4, CaMKII, AMPK, and PKB/Akt significantly ↑ post therapy in SCI but not AB

Note: ↑ = increase; ↓ = decrease; ↔ = no change; AB = able-bodied controls; ACE = arm cycling ergometry; AIS = American Spinal Injury Association Impairment Scale (A: complete; B: sensory incomplete, C: motor complete, D: motor incomplete, E: normal); AUC = area under the curve; AMPK = adenosine monophosphate kinase; CaMKII = calmodulin-dependent protein kinase; DXA = dual-energy x-ray absorptiometry; EE = energy expenditure; EHIC = euglycemic hyperinsulinemic clamp; FES-LEC = functional electrical stimulation-lower extremity cycling FI = fasting insulin; FG = fasting glucose; FFM = fat-free mass; FM = fat mass; GLUT4 = glucose transporter-4; HOMA = homeostasis model assessment; HOMA2 = homeostasis model assessment-2; IMF = intramuscular fat; IR = insulin resistance; MRI = magnetic resonance imaging; NMES-RE = neuromuscular electrical stimulation-induced resistance exercise; TSI = time since injury; LOI = level of injury; min = minutes; n-PA = non-physically active; PGC-1a = peroxisome proliferator-activated receptor coactivator 1 alpha; PA = physically active; PG = plasma glucose; PI = plasma insulin; PSCI = paraplegic spinal cord injury; PBK/Akt = protein kinase B; RT = resistance training; SCI = spinal cord injury; Si = insulin sensitivity; y = years.
*Method of EE measurement not listed in study

FES-lower extremity cycling (LEC), Griffin et al.[97] found subjects had significantly lower glucose, higher insulin, and lower inflammatory markers, while de Groot et al.[98] found a positive correlation between increasing cardiopulmonary fitness and insulin sensitivity. In Gorgey et al.,[104] increased muscle activity via spasticity was associated with improved resting metabolic rate, insulin sensitivity, lipid profile, and increased FFM. A systematic review by Farrow et al.[100] concluded improvements in peripheral and hepatic insulin sensitivity following FES-LEC and arm cycling ergometry (ACE), respectively. Nightingale et al.[88,101] reported fasting insulin was reduced by 14% and pancreatic beta cell function by 24% via OGTT and HOMA2, respectively, following 6 weeks of ACE in 20 subjects with chronic SCI. Bresnahan et al.[102] found a 30% increase in hepatic insulin sensitivity measured by HOMA2 after people with SCI completed 10 weeks of ACE. Increased exercise activity in persons with SCI has been reported to raise crucial skeletal muscle proteins (e.g., GLUT4, AMPK, and PGC-1a) involved in glucose transport and energy metabolism.[9,103] Gorgey et al.[103] studied the changes in these proteins in nine men with chronic SCI after 16 weeks of FES-LEC or ACE. At the conclusion of the study, the investigators found a two- to four-fold increase in these glucose transport proteins.[103] Taken together, these data show that greater muscle activity has a beneficial effect on "insulin sensitivity," although some of these findings may reflect non–insulin-mediated glucose transport in response to acute exercise.

Conclusion

The current review examined "estimated" insulin resistance and T2DM after SCI with several assessment methods and indices to evaluate carbohydrate metabolism. The prevalence of both insulin resistance and T2DM in persons with SCI is staggering and suggests that T2DM is at epidemic proportions within the population with SCI. While it is known that the prevalence of T2DM is greater in persons with SCI than those without SCI using standard diagnostic criteria as outlined in this review, it is unknown if the current methods used to assess disorders of carbohydrate metabolism in persons with SCI are appropriate as they may underestimate the true occurrence. Specifically, it remains unknown if the current cutoff values used to identify prediabetes, T2DM, and elevated fasting glucose levels correctly capture and diagnose these metabolic comorbidities. This is an area in which future research is needed. Nonetheless, raising awareness can increase the recognition for insulin resistance and T2DM, and lifestyle interventions using diet and exercise can help treat and prevent these disorders in persons with chronic SCI.

Conflicts of Interest

The authors declare no conflicts of interest.

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